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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/806,635	06/04/2001	Carola Dony	HUBR-1186 (10102735)	3339

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EXAMINER	
ANDRES, JANET L	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/806,635	DONY ET AL.
Examiner	**Art Unit**
Janet L. Andres	1646

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-34* is/are pending in the application.

4a) Of the above claim(s) *30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20,22-25,27-29,33 and 34* is/are rejected.

7)☐ Claim(s) *21 and 26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, pharmaceutical agents and methods of use, in Paper No. 11 is acknowledged. The requirement for an election of osteoinductive species is withdrawn in response to Applicant's arguments that the species are obvious, each over the other. Applicant's amendment to claim 33 results in the inclusion of claims 33 and 34 in this group. The restriction requirement of paper no. 10 is made final. Claims 18-34 are pending in this application. Claims 30-32 are withdrawn from consideration as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 18 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. patent 5,770,366 (Bogdahn et al., 1988) in view of U.S. patent 4,919,929 (Beck, 1990).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The '366 patent teaches melanoma-inhibiting protein (MIA) and teaches that it inhibits cancer cell division as well as proliferation of peripheral blood lymphocytes (column 4, lines 36-65). The '366 patent fails to teach compositions comprising this protein and the biocompatible matrices claimed in claim 18. The '929 patent teaches that matrices comprising polyanhydrides, polylactic acid-co-glycolic acid, or collagen can be used as a delivery system for antigens to produce antibodies in animals (column 2, lines 55-67 and column 3, lines 43-55). The '929 patent fails to teach combinations of MIA with such matrices. However, it would be obvious to one of ordinary skill in the art to combine the teachings of the '366 patent with the '929 patent to generate compositions comprising MIA and polyanhydrides, polylactic acid-co-glycolic acid, or collagen. One of ordinary skill would be motivated to do so because the '366 patent teaches in column 4, lines 16-39 that such antibodies are desirable, and the '929 patent teaches an advantageous way of preparing antibodies.

4. Claims 18 and 23 are additionally rejected under 35 U.S.C. 103(a) as being unpatentable over the '366 patent in view of the 1992 BioRad catalogue, pp. 26 and 32.

The '366 patent teaches as set forth above but fails to teach compositions comprising MIA and hydroxylapatite or heparin. The BioRad catalogue teaches adsorption of proteins onto heparin (p. 26, column 1) and hydroxylapatite (p. 32) for purposes of purification. The BioRad catalogue fails to teach purification of MIA and thus fails to teach a composition comprising MIA and heparin or hydroxylapatite. However, it would be obvious to one of ordinary skill in the art to combine the teachings of the BioRad catalogue with those of the '366 patent to

generate such a composition. One of ordinary skill would be motivated to do so because the '366 patent teaches that the protein is useful for inhibition of cancer cell growth and as an immunosuppressive agent (column 4, lines 40-65), and the BioRad catalogue provides a means for obtaining the protein.

Combinations with alginate, tricalcium phosphate, hyaluronic acid, and calcium sulfate are not obvious over the prior art because such compositions are used *in vivo* for bone and connective tissue implants. See, for example, U.S. patent 6,331,312 (Lee et al., 2001), which teaches such uses in column 9, lines 25-53. There is no motivation in the prior art to combine MIA with such materials, since, while MIA is well known in the art, it is known as a cancer inhibitor and diagnostic agent, and the art does not teach that it would be useful for such implants.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 18, 23, 24, and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention.

The factors to be considered have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte*

Forman, (230 USPQ 546 (Bd Pat. App. & Int. 1986)); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The claims are drawn to pharmaceutical compositions of MIA and biocompatible matrices (claims 18 and 23) and methods using them to grow bone or cartilage (claims 24 and 33).

Because claims 18 and 23 are drawn to a pharmaceutical composition, they indicate a therapeutic use for the composition. MIA is known to be useful for the inhibition of cancer cell growth and as an immunosuppresant (see the '366 patent, above) and as a marker for cartilage disease (U.S. patent 6,150,118, Basserhof et al., 2000). MIA in combination with the claimed matrices could not be used for this purpose, however, since such matrices are used *in vivo* as bone implants (see the '312 patent). The instant specification fails to provide sufficient guidance for the use of MIA in such a matrix to grow bone or cartilage, and thus fails to provide enablement for either the pharmaceutical compositions of claims 18 and 23 or the methods of claims 24 and 33. No osteogenic or chondrogenic activity is set forth for MIA. What is shown in Table I (p. 8) is that MIA is synergistic with Hedgehog for the induction of the bone marker alkaline phosphatase. Applicant states on lines 6-8 that MIA had no activity by itself. Table 2, p. 10, shows only stimulation of DNA incorporation into primary chondrocytes. This is not sufficient guidance to indicate that MIA could induce cartilage production; fetal calf serum, which also induces DNA incorporation (table 2) has no such effect. The examples on pp. 9-14 appear to be proposed experiments only; no results are shown. They therefore do not provide adequate guidance as whether MIA could be used to grow bone or cartilage, but are merely an invitation to the artisan to use the current invention as a starting point for further

experimentation. Thus the specification does not provide working examples or other objective evidence to indicate that MIA alone could be used to grow either bone or cartilage. The prior art fails to provide compensatory teachings. The '118 patent, in column 6, lines 25-54, teaches that MIA can be used as a marker for cartilage disease but provides no guidance as to its physiological function; its presence in disease does not provide an indication as to its role. Thus, since the instant specification provides no objective evidence or guidance that would allow one of skill to predictably use MIA as claimed, and the prior art provides no compensatory teachings, it would require undue experimentation for the skilled artisan to use MIA in the claimed matrices to grow bone or cartilage.

7. Claims 19, 20, 22, 25, 27-29, and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are drawn to compositions and methods involving osteoinductive proteins. Thus the claims encompass all proteins capable of inducing bone growth. Applicant has not, however, described the characteristics of such proteins so that one of skill in the art would conclude that Applicant was in possession of the genus of osteoinductive proteins. Applicant indicates in the specification that hedgehog proteins and BMPs are osteoinductive (p. 1, lines 20-24). However, Applicant has not indicated any common structural or functional features that would allow one of skill in the art to identify other osteoinductive proteins, based on the disclosure of these two families. BMPs and hedgehogs are structurally distinct and Zhou et al. (Genes and Development, 1997, vol. 11, pp. 2191-2203)) teaches that they function at different

levels and through different receptors (p. 2196, figure 4J, figure legend, p. 2197, p. 2199, figure 7). Thus the teaching that members of these two families are osteoinductive does not indicate to the skilled artisan what characteristics are indicative of osteoinductive proteins; they do not have common structural or functional characteristics. Thus the disclosure of BMPs and hedgehog proteins does not identify relevant characteristics or common features so that one of skill in the art would recognize that Applicant was in possession of the genus of osteoinductive proteins, and methods of using them, as broadly claimed.

Claim Objections

8. Claims 23, 28, and 29 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 23 depends from claim 18, but includes heparin and polylactic coglycolid derivatives, which claim 18 does not. Since the claims are drawn to MIA and at least one matrix component, claim 23 encompasses compositions, MIA and heparin or polylactic coglycolid derivates, that are not within the scope of claim 18.

Claim 28 depends from claim 25, and requires that the MIA be in a biocompatible matrix. However, claim 25 is drawn to a method using the composition of claim 18. That composition comprises MIA in a biocompatible matrix and thus claim 28 is not further limiting.

Claim 29, like claim 29, is drawn to a method using the composition of claim 18. However, like claim 23, it includes matrices that are not within the scope of claim 18.

9. Claim 34 is objected to because of the following informalities: "is used" appears to have been included at the end of the claim inadvertently. Appropriate correction is required.

Allowable Subject Matter

10. Claims 21 and 26 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims and, for claims 28, 29, and 34, if rewritten to overcome the objections set forth above.

CLAIMS 18-20, 22-25, 27-29, 33, AND 34 ARE REJECTED. CLAIMS 21 AND 26 ARE OBJECTED TO.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet Andres, Ph.D., whose telephone number is (703) 305-0557. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564. The fax phone number for this group is (703) 872-9306 or (703) 872-9307 for after final communications.

Communications via internet mail regarding this application, other than those under U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[yvonne.eyler@ uspto.gov]**.

All Internet email communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly

set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Janet Andres, Ph.D.
Patent Examiner

March 23, 2003